Office Action Summary	Application No.	Applicant(s)
	10/690,199	ASTSATUROV ET AL.
	Examiner	Art Unit
	WU-CHENG SHEN	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11-15,18-22,24-26,28-30 and 32-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,11-15,18-22,24-26,28-30 and 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim amendments filed on 06/14/2011 have been entered

Claims 2-3, 8-10, 16, 17, 23, 27, and 31 are cancelled. Claims 1, 36, 38 and 39 are amended. Claims 1, 4-7, 11-15, 18-22, 24-26, 28-30, 32-39 are pending and currently under examination.

This application 10/690,199 filed on Oct. 21, 2003 claims benefit of provisional application 60/420,425 filed on Oct. 22, 2002. The publication number of this application 10/690,199 is US 2004/0223949 A1, published on Nov. 11, 2004.

Claim Objections

1. Previous objection of claim 36 because of recitation of "the peptides YLEPGPVTV and IMDQVPFSV" without citation of SEQ ID NO is ***withdrawn*** because the claims have been amended.

Claim Rejection – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Previous rejection of claims 1, 4-7, 11-15, 18-22, 24-26, 28-30, 32-39 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 06/14/2011 reads as follows: A method for treating melanoma comprising: (a) administering to a mammal having melanoma a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the mammal develops an immune response against the tumor antigen; and, (b) subsequently administering at least l0 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal.

3. Claims 1, 4-7, 11-15, 18-22, 24-26, 28-30, 32-39 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 06/14/2010.*

Amended claim 1 filed on 06/14/2011 reads as follows: A method for treating melanoma comprising: (a) administering to a mammal having melanoma a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the mammal develops an immune response against the tumor antigen; and, (b) subsequently administering at least l0 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal.

Amended claim 38 filed on 06/14/2011 reads as follows: The method of claim 1 further comprising examining the mammal to identify evidence of melanoma progression following step (b).

Amended claim 39 filed on 06/14/2011 reads as follows: The method of claim 38 wherein the mammal is examined radiologically.

It is noted that the amended claim 1 does not recite any "evidence of melanoma progression" before step (b), and amended claim 38 recites "examining the mammal to identify evidence of melanoma progression following step (b)". Claims 38 and 39 as amended require

that "following step (b)" recited in claim 1, "evidence of melanoma progression" is to be identified by radiological examination. In other words, claims 38 and 39 as amended require the completion of the active steps (a) and (b) recited in claim 1 of a method for treating melanoma to show "evidence of melanoma progression", which is to be identified by radiological examination. It is unclear what therapeutic effect(s) or lack of therapeutic effect(s) of claimed methods are intended to be for claim 1, and its dependent claims, in light of the limitations "evidence of melanoma progression" to be identified by radiological examination required by the amended claims 38 and 39.

Claims 4-7, 11-15, 18-22, 24-26, 28-30, 32-39 depend from claim 1.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

4. Claims 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This rejection is necessitated by claim amendments filed on 06/14/2010.*

Claim 38 filed on 06/14/2011 reads as follows: The method of claim 1 further comprising examining the mammal to identify evidence of melanoma progression following step (b).

Claim 39 filed on 06/14/2011 reads as follows: The method of claim 38 wherein the mammal is examined radiologically.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

It is noted that there is no support in the specification for the amended limitations recited in amended claims 38 and 39 filed on 06/14/2011. The specification does not provide any description what is/are the "evidence of melanoma progression" following step (b) to be identified by radiological examination. Applicant's remarks filed on 06/14/2011 do not provide any citation from specification originally filed on 10/21/2003 that support the limitations recited in amended claims 38 and 39.

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Morton et al.** (Morton et al., Vaccine therapy for malignant melanoma, *CA Cancer J Clin.* 46(4):225-44, 1996). Applicant's arguments filed 06/14/2011 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 7-17 of the office action mailed on 12/15/2010. It is noted that claims 38 and 39 are no longer included in this maintained rejection due to claim amendments filed on 06/14/2011. In this regard, more elaboration has been provided in the rejection under 35 U.S.C. 112, second paragraph, and the rejection under 35 U.S.C. 112, first paragraph documented above in this office action.

For the clarity of record, previous rejection for the reasons of record advanced on pages 7-17 of the office action mailed on 12/15/2010 is reiterated below, with revisions addressing claim amendments filed on 06/14/2011.

Amended claim 1 filed on 06/14/2011 reads as follows: A method for treating melanoma comprising: (a) administering to a mammal having melanoma_a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical

agent such that the mammal develops an immune response against the tumor antigen; and, (b) subsequently administering at least l0 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal.

Paoletti teaches attenuated recombinant viruses containing DNA coding for a cytokine and/or a tumor (or melanoma) associated antigen, as well as methods and compositions employing the viruses. Paoletti teaches that the recombinant viruses can be NYVAC or ALVAC recombinant viruses. The DNA can code for at least one of: human melanoma-associated antigen (MAGE-1; MZE-2) ; IL-2; IFNγ; IL-4; GMCSF; IL-12; B7; erb-B-2, and carcinoembryonic antigen (CEA). Paoletti teaches that the recombinant viruses and gene products are useful for cancer therapy (See abstract, and lines 40-45, column 13, Paroletti). Paoletti teaches that the immune responses in a mammalian host against tumor cells are mediated by T-cells, particularly cytotoxic T lymphocytes (CTLs); white blood cells capable of killing tumor cells and virus-infected cells (column 7, lines 55-57). Furthermore, Paoletti teaches the administration of a cytokine secreted from modified tumor cells can subsequently be utilized for active immunization. The therapeutic potential for such an administration is based on the ability of cytokines to alter the presentation of TAAs to achieve systematic anti-tumor activity (See column 16, lines 3-8). Paoletti teaches that the vaccines or compositions can be co-administered or *sequentially* administered with other anti-neoplastic, anti-tumor or anti-cancer agents and/or with agents which reduce or alleviate ill effects of antineoplastic, anti-tumor or anti-cancer agents; again taking into consideration such factors as the age, sex, weight, and condition of the particular patient, and, the route of administration (See line 55-616, column 13, Paroletti)

Paoletti also teaches (1) viral vectors including poxvirus, vaccinia virus, and avipox virus (See, for instances, column 2, background of the invention, second paragraph; claims 1-8); NYVAC, ALVAC, and TROVAC based recombinant viruses expressing TAAs plus or minus specific cytokines for adoptive immunotherapy (See column 15, lines 45-48, column 17, lines 8-9); as well as canarypox virus (column 16, line 55) and fowlpox virus (column 16, line 64); (2) expression of tumor antigens --- CEA, carcinoembryonic antigen, (columns 70-77, example 17); p53 (columns 65-68, example 15); MAGE-1 (columns 68-70, example 16); and cytokines --- human INFγ (columns 83-84, example 21), IL-2 (column 79-80, example 19) in both ALVAC-based viral vectors (which encompasses ALVAC or ALVAC(2) recited in claim 29-34 of instant application), and NYVAC based viral vectors.

Paoletti does not explicitly teach **(i)** a melanoma-associated tumor antigen or INF-α2b as the sole active pharmaceutical agent recited in amended claim 1, and gp100 peptides recited in newly added claim 36 as the sole active pharmaceutical agent, and **(ii)** subsequently administering at least 10 MU/m^2/day INF-α2b recited in step (b) of claim 1 for cancer vaccine regimen.

(i) Ematge et al. teaches peptides, including tumor-associated antigen gp100, and nucleic acid sequences encoding such peptides for use in diagnosing, treating, or preventing melanoma (See abstract, and paragraph [0010], Ematge et al. 2003). Ematge et al. teaches the following statements: "While the compositions of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents (i.e., other immunogenic targets, co-stimulatory molecules, adjuvants). When administered as a combination, the individual components can be formulated as separate

compositions administered at the same time or different times, or the components can be combined as a single composition (See paragraph [0094] by Ematge et al. 2003, which is verbatim of [0074] of 2004/0223949, publication of instant application). Ematge et al. teaches a kit comprising a composition of the present invention is also provided. The kit can include a separate container containing a suitable carrier, diluent or excipient. The kit can also include an additional anti-cancer, anti-tumor or antineoplastic agent and/or an agent that reduces or alleviates ill effects of antineoplastic, anti-tumor or anti-cancer agents for co- or sequential-administration. Additionally, the kit can include instructions for mixing or combining ingredients and/or administration (See paragraph [0100], Ematge et al. 2003).

(ii) With regard to administering at least 10 MU/m^2/day INF-α2b recited in step (b) of claim 1, and various vaccination of 10 MU/m^2/day INF-α2b recited in claims 18-22, 28, and 29, **Kirkwood et al.** teach high dose INF-α2b, as the sole active pharmaceutical agent administered intravenously, in the treatment of patients with melanoma. Specifically, Kirkwood et al. teach high dose of INF-α2b (20 megaunits [MU]/m^2/d IV (intravenously) x 5 days a week for four week and 10 MU/m^2 SC (subcutaneously) three times per week [TIW] x 48 weeks), which was approved as adjuvant therapy for high-risk melanoma by the United States Food and Drug Administration (FDA) in 1995 (See first paragraph of Introduction, Kirkwood et al., 2001). The treatment significantly prolongs relapse-free survival and overall survival in high-risk melanoma patient. Kirkwood et al. teaches that dose reduction in the INF-α2b was performed in accordance with the common toxicity criteria established by the National Cancer Institute Treatment Evaluation Program. If criteria dictating dose modification were met, then treatment was withheld until recovery from toxicity. Treatment Statistical Analysis was resumed with a

33% dose reduction after the first treatment interruption for toxicity; a 66% dose reduction (i.e. at least 6 MU/m^2/day INF-α2b as recited in claim 29 of instant application) was required after a Efficacy comparisons between the GMK and IFNα2b arms were second treatment interruption for toxicity (See bridging paragraph, page 2371-2372, Kirkwood et al., 2001). Kirkwood et al. do not explicitly teach combining high dose INF-α2b cytokine therapy subsequently to nucleic acid expressing a melanoma-associated antigen as a treatment of melanoma.

With regard to *subsequently* administering of interferon alpha 2b (IFN-α2b) recited in step (b) of claim 1, **Morton et al.** teaches various combinations of vaccine therapy protocols for treating malignant melanoma (See title and abstract, Morton et al., 1996). Morton et al. teaches some immunogenic antigens identified in human melanoma cells (See Table 1, shown below, Morton et al., 1996).

Table 1
Some Immunogenic Antigens Identified in Human Melanoma Cells*

Common Tumor-Associated Antigens (TAA)	Melanoma-Associated Antigens (MAA)
TAA are found not only in melanoma but also in kidney, lung, breast, and other solid neoplasms	MAA are found primarily in melanocytes/melanoma (and rare neoplasms of neural crest origin)
†Urinary TAA (glycoprotein 90)[18]	†Lipoprotein190[19]
†Fetal antigen (glycoprotein 70)[17]	Tyrosinase[20]
†810 peptide (43 kd)[20]	MART-1/Melan A[21,22]
†MAGE 1[23]	Glycoprotein 75 (gp 75.TRP)[24]
†MAGE 3[23]	Glycoprotein 100 (gp 100/pmel 17)[24,25]
†GM2[16]	High molecular weight melanoma antigen[26,36]
†GD2[16]	
†O-acetyl GD3[16]	
†GM3[15]	

*All of these antigens have been identified in the three melanoma cell lines used in the John Wayne Cancer Institute's living allogeneic melanoma cell vaccine (CancerVax). Some have not yet been fully characterized.

†Antibody responses to these antigens have been demonstrated in the serum of patients receiving active immunotherapy with CancerVax.

Morton et al. teaches that "Other Vaccine Studies in Patients with Stage IV Melanoma: In several phase I/II studies, Mitchell's group tested preparations of two mechanically disrupted melanoma cell lines (Melacine) injected subcutaneously in combination with the adjuvant DETOX. Median overall survival of the 106 patients was 12.2 months, but 20 patients (19 percent) had objective clinical regression of tumor masses, five with complete responses. The median duration of response was 46 months. Clinical response correlated with an increase in the level of cytotoxic T-cell precursors in the blood as well as a partial match of the patient's HLA phenotype with vaccine cell lines" (See bridging paragraph, pages 232-233, Morton et al., 1996).

Morton et al. further teaches "*Subsequent administration of interferon alfa-2b (IFN α-2b)* at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 patients who failed Melacine treatment regardless of their HLA phenotype. Based on these results, a national confirmatory phase III trial will compare Melacine plus IFN alfa-2b with IFN alfa-2b alone. This trial will include 300 patients and is scheduled to begin this year" (See right column, page 233, Morton et al., 1996).

It is noted that the combination of the teachings by Paoletti regarding the DNA vaccines or compositions can be co-administered or *sequentially administered* with other anti-neoplastic, anti-tumor or anti-cancer agents and/or with agents which reduce or alleviate ill effects of antineoplastic, anti-tumor or anti-cancer agents; again *taking into consideration such factors as the age, sex, weight, and condition of the particular patient, and, the route of administration* (See line 55-616, column 13, Paroletti) and the teachings by Morton regarding "*Subsequent administration of interferon alfa-2b (IFN alpha-2b)* at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 patients who failed Melacine treatment regardless of their HLA phenotype" render the administration of DNA vaccine recited in step (a) of claim 1 and subsequently administering interferon alpha 2b recited in step (b) of claim 1 *prima facie* obvious. It is worth noting that *Morton et al. teaches that melanoma-associated antigens (MAA) are weak antigens, and melanoma patients receiving therapeutic vaccines are usually immunized repeatedly for prolonged periods (See right column, page 228, Morton et al., 1996), which provides the motivation for a skilled artisan to use DNA vaccine taught by Paoletti instead of using the cell lysate of mechanically disrupted melanoma cell lines (Melacine) taught by Morton et al.*

With regard to absence of repeating step (a) after step (b) recited in claim 35 and step (b) occurs between 1.5 and 17 months after step (a) recited in claim 37, these limitations are optimization of vaccination and obvious variants of the vaccination regimens taught by combined teachings of Morton et al. (See Figures 2 and 3, pages 231-232, Morton et al.) and Kirkwood et al. (See patients and methods, pages 2371-2372, Kirkwood et al.). In this regard, Applicant's attention is directed to the statements provided in MPEP § 2131.03.

2144.05 [R-5] Obviousness of Ranges

See MPEP § 2131.03 for case law pertaining to rejections based on the anticipation of ranges under 35 U.S.C. 102 and 35 U.S.C. 102/103.

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable there over because, among other reasons,

there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention to substitute the cytokine (including INFγ and IL-2) taught by combined teachings of Paoletti and Ematge et al., regarding treating melanoma by administering nucleic acid expressing a melanoma-associated antigen gp100, and subsequently administering a high dose INF-α2b taught by Kirkwood et al. and Morton et al., and to follow the melanoma vaccination treatment regimens taught by Morton et al. and Kirkwood et al. to arrive at the claimed inventions of a method of treating melanoma as recited in claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37-39 of instant application.

One having ordinary skill in the art would have been motivated to substitute the cytokine (including INFγ and IL-2) taught by Paoletti, Emtage et al., and Morton et al. in treating melanoma with a high dose INF-α2b taught by Kirkwood et al., and to follow the cancer vaccination treatment regimens taught by Aarts et al. and Kirkwood et al. because (i) Morton et al specifically teaches subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m2 subcutaneously, three times per week, induced responses in eight of 18 melanoma patients who failed Melacine treatment regardless of their HLA phenotype, and (ii) Emtage et al specifically teaches peptides, including tumor-associated antigen gp100, and nucleic acid sequences encoding such peptides for use in diagnosing, treating, or preventing melanoma, and the compositions can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents (i.e., other immunogenic targets, co-stimulatory molecules, adjuvants).

There would have been a reasonable expectation of success given (i) combinatory cancer therapy with expression of a melanoma-associated tumor antigen and expression of a cytokine (including INFγ) either co-administered or sequentially administered, by the teachings of Paoletti, (ii) identification of multiple melanoma-associated antigen and expression of nucleic acid encoding the antigens in treating melanoma, by the teachings of Emtage et al. (Examples 1-4), (iii) the results of high dose of INF-α2b in the treatment of melanoma by the teachings of Kirkwood et al to achieve a tumor antigen specific immune response involving enhanced T cell response, and (iv) various combinations of vaccine therapy protocols for treating malignant melanoma, some immunogenic antigens identified in human melanoma cells, and subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m^2 subcutaneously,

three times per week, induced responses in eight of 18 melanoma patients who failed Melacine treatment regardless of their HLA phenotype, by the teachings of Morton et al. (See title, Table 1, and page 233).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and ***Response to Applicant's arguments***

(i) Applicant argues that the Applicants have addressed each of the cited reference individually but also explained how the deficiencies in those individual references render the combination as a whole ineffective. It is the Applicants' view that this approach is not inconsistent with either In re Keller or In re Merck. It is only after a determination of what: each reference may or may not teach has been made that the references may be considered as a combination. Applicants' approach is similar to the manner in which the rejections are presented in the Office Action (See page 7 of Applicant's remarks filed on 06/14/2011).

In response, the Examiner maintains the position that the combined teachings of Paoletti, Emtage et al., and Morton et al. in treating melanoma with a high dose INF-α2b taught by Kirkwood et al. render the claimed method *prima facie* obvious. With regard to the arguments that "deficiencies in those individual references renders the combination as a whole ineffective", the Examiner notes that the claimed methods do not require any specified therapeutic efficacy. To the contrary, claims 38 and 39 require the completion of the active steps (a) and (b) recited in claim 1 of a method for treating melanoma to show "evidence of melanoma progression", which is to be identified by radiological examination.

As stated in the maintained rejection, it is noted that the combination of the teachings by Paoletti regarding the DNA vaccines or compositions can be co-administered or *sequentially administered* with other anti-neoplastic, anti-tumor or anti-cancer agents and/or with agents which reduce or alleviate ill effects of antineoplastic, anti-tumor or anti-cancer agents; again *taking into consideration such factors as the age, sex, weight, and condition of the particular*

patient, and, the route of administration (See line 55-616, column 13, Paroletti) and the teachings by Morton regarding "*Subsequent administration of interferon alfa-2b (IFN alpha-2b)* at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 patients who failed Melacine treatment regardless of their HLA phenotype" render the administration of DNA vaccine recited in step (a) of claim 1 and subsequently administering interferon alpha 2b recited in step (b) of claim 1 *prima facie* obvious.

(ii) Applicants notes that the instantly claimed methods require administration of "at least 10 MU/m^2/day interferon alpha 2b (INF-α2b) as the sole active pharmaceutical agent to the mammal". As described in Applicants' specification, at least 10 MU/m^2/day IFN-α2b would be understood by those of Skill in the art to be a "high-dose" IFN-α2b protocol (e.g. Applicants' paragraph [0072] and Kirkwood et al. *J. Clin. Oncol.* 18:2444-2458 (2000)). Applicants' claimed high-dose regimen is understood by those of skill in the art to be very different from a "low-dose" regimen, such as $5x10^6$ U/m^2 as described by Morton. For example, it is know that a high-dose regimen may be associated with complications from toxicity (e.g., Applicants' paragraph [0083]), which is not observed when using low-dose regiments (e.g. Kirwood, *supra*, p. 2445 ("~...given the substantial toxicities associated with high-dose IV IFNα2b, alternative regimens have also been widely investigated.")) (See pages 8-9 of Applicant's remarks filed on 06/14/2011).

In response, the Examiner notes that the claimed method encompasses treating any stage and/or degree of severity of melanoma with any spectrum of risk-and-benefit assessment for treatment. In this regard, as clearly documented in the maintained rejection, **Kirkwood et al.** teach high dose INF-α2b, as the sole active pharmaceutical agent administered intravenously, in the treatment of patients with melanoma. Specifically, Kirkwood et al. teach high dose of INF-α2b (**20 megaunits [MU]/m^2/d** IV (intravenously) x 5 days a week for four week and 10 MU/m^2 SC (subcutaneously) three times per week [TIW] x 48 weeks), which was approved as adjuvant therapy for **high-risk melanoma** by the United States Food and Drug Administration (FDA) in 1995 (See first paragraph of Introduction, Kirkwood et al., 2001). *The treatment significantly prolongs relapse-free survival and overall survival in high-risk melanoma patient.* Kirkwood et

al. teaches that dose reduction in the INF-α2b was performed ***in accordance with the common toxicity criteria established by the National Cancer Institute Treatment Evaluation Program***. If criteria dictating dose modification were met, then treatment was withheld until recovery from toxicity. Treatment Statistical Analysis was resumed with a 33% dose reduction after the first treatment interruption for toxicity; a 66% dose reduction (i.e. at least 6 MU/m^2/day INF-α2b as recited in claim 29 of instant application) was required after a Efficacy comparisons between the GMK and IFNα2b arms were second treatment interruption for toxicity (See bridging paragraph, page 2371-2372,). Kirkwood et al. do not explicitly teach combining high dose INF-α2b cytokine therapy subsequently to nucleic acid expressing a melanoma-associated antigen as a treatment of melanoma.

(iii) Applicants maintain that the line of reasoning behind this second "motivation" is also misplaced. The Office Action merely concluded that "[o]ne having ordinary skill in the art would have been motivated to substituted the cytokine (including IFNγ and IL-2) taught by Paoletti" because of what each reference teaches individually. The Office Action has not explained why, for example, one of ordinary skill in the art would move from the non-toxic and apparently successful low-dose regimen of Morton to Applicants instantly claimed high-dose regimen. No actual motivation or reason that would have driven one of ordinary skill in the art to make the alleged combination has been provided in the Office Action (See page 10 of Applicant's remarks filed on 06/14/2011).

In response, as responded in **(ii),** it is emphasized that claimed "high-dose" regimen in the maintained 103(a) rejection is taught by Kirkwood et al. (2001), not by Morton et al. as Applicants continued to argue. With regard to the reason why "one of ordinary skill in the art would move from the non-toxic and apparently successful low-dose regimen of Morton to "high-dose" regimen taught by Kirkwood et al. (2001), **Kirkwood et al.** specifically teach high dose INF-α2b, as the sole active pharmaceutical agent administered intravenously, in the treatment of patients with melanoma. Specifically, Kirkwood et al. teach high dose of INF-α2b (**20 megaunits [MU]/m^2/d** IV (intravenously) x 5 days a week for four week and 10 MU/m^2 SC (subcutaneously) three times per week [TIW] x 48 weeks), which was approved as adjuvant

therapy for **high-risk melanoma** by the United States Food and Drug Administration (FDA) in 1995 (See first paragraph of Introduction, Kirkwood et al., 2001). ***The treatment significantly prolongs relapse-free survival and overall survival in high-risk melanoma patient.***

(iv) Applicant states that, as explained above, Applicants maintain that the Office Action has merely concluded that one of ordinary skill in the art would have combined the disclosures of the cited references m produce Applicants' claimed methods, The Office Action not explained why "one of ordinary skill in the art would have any reason, to try" (e.g., as in Rolls-Rovce) Applicants' claimed method, as legally required. The Office Action merely concluded that given the content of individual references, it would have been done. This is clearly an improper hindsight (See page 12 of Applicant's remarks filed on 06/14/2011).

In response, it is noted that the maintained 103(a) rejection is **not** based on "obvious to try" scenario. The Examiner had noted on page 22 of the Non-Final office action mailed on 12/15/2010 that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Paoletti, Emtage et al., Kirkwood et al., and Morton et al. have been clearly set forth above in this office action. Furthermore, as responded in **(ii)**, the Examiner notes that the claimed method encompasses treating any degree and/or stage of melanoma with any spectrum of risk-and-benefit assessment for treatment. Kirkwood et al. (2001) specifically discloses that the "high-dose" of INF-α2b treatment ***significantly prolongs relapse-free survival and overall survival in high-risk melanoma patient.*** Therefore, the arguments that "This is clearly an improper hindsight" have been fully considered and found not persuasive. Accordingly, the Examiner maintains the position that one having ordinary skill in the art would have been motivated to substitute the cytokine (including INFγ and IL-2) taught by Paoletti, Emtage et al., and Morton et al. in treating melanoma with a high dose INF-α2b taught by Kirkwood et al., and to follow the cancer vaccination treatment regimens taught by Aarts et al. and Kirkwood et al. because (i) Morton et al specifically teaches subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m2 subcutaneously, three times per week, induced responses in eight of 18 melanoma patients who failed Melacine treatment regardless of their HLA phenotype, and (ii)

Emtage et al specifically teaches peptides, including tumor-associated antigen gp100, and nucleic acid sequences encoding such peptides for use in diagnosing, treating, or preventing melanoma, and the compositions can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compositions or agents (i.e., other immunogenic targets, co-stimulatory molecules, adjuvants).

6. Claims 24-26 and 36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Morton et al.** (Morton et al., Vaccine therapy for malignant melanoma, *CA Cancer J Clin.* 46(4):225-44, 1996), as applied to claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37 above, and further in view of **Kawakami et al.** (Kawakami et al., US Patent No. 5,844,075, issued on 12/01/1998).

Previous rejection is ***maintained*** for the reasons of record advanced on pages 17-23 of the office action mailed on 12/15/2010.

For the clarity of record, previous rejection for the reasons of record advanced on pages 17-23 of the office action mailed on 12/15/2010 is reiterated below, with revisions addressing claim amendments filed on 06/14/2011.

Amended claim 1 filed on 06/14/2011 reads as follows: A method for treating melanoma comprising: (a) administering to a mammal having melanoma a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the mammal develops an immune response against the tumor antigen; and, (b) subsequently administering at least 10 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal.

The teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton have been discussed in the preceding section of the rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37 under 35 U.S.C. 103(a) as being unpatentable over Paoletti in view of Emtage et al., Kirkwood et al., and Morton et al. It has been noted the limitations recited in claim 36 are obvious variant of the teachings by Morton et al. regarding various subsequent booster vaccinations with a melanoma-associated tumor antigen, which includes gp100 taught by Emtage et al. and Morton et al., and/or a cytokine.

None of Paoletti, Emtage et al., Kirkwood et al. and Morton et al. teaches SEQ ID No:2 and SEQ ID No:3 of gp100 recited in claims 24-26 and 36.

However, at the time of filing of instant application, the gp100 as a melanoma-associated tumor antigen recited in claims 11-13 and 23, and SEQ ID No:2 and SEQ ID No:3 of gp100 recited in claims 24-26, were known in the art. For instant, **Kawakami et al.** teaches immunogenic peptides derived from melanoma antigen designated gp100, including SEQ ID No: 2 and SEQ ID No: 3 recited in claims 24-26 and 36 of instant application (See below for the

alignment of SEQ ID No: 2 of instant application with SEQ ID No: 84 of Kawakami et al., and the alignment of SEQ ID No: 3 of instant application with SEQ ID No: 104 of Kawakami et al.).

SEQ ID No: 2

```
RESULT 1
US-08-417-174-84
; Sequence 84, Application US/08417174
; Patent No. 5844075
;  GENERAL INFORMATION:
;    APPLICANT:  KAWAKAMI, YUTAKA; ROSENBERG,
;    APPLICANT:  STEVEN A.
;    TITLE OF INVENTION:  MELANOMA ANTIGENS AND
;    TITLE OF INVENTION:  THEIR USE IN DIAGNOSTIC AND THERAPEUTIC
;    TITLE OF INVENTION:  METHODS
;    NUMBER OF SEQUENCES:  126
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  MORGAN & FINNEGAN, L.L.P.
;      STREET:  345 PARK AVENUE
;      CITY:  NEW YORK
;      STATE:  NEW YORK
;      COUNTRY:  USA
;      ZIP:  10154
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  FLOPPY DISK
;      COMPUTER:  IBM PC COMPATIBLE
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  ASCII
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/417,174
;      FILING DATE:  05-APR-1995
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/231,565
;      FILING DATE:  22-APR-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  CAROL M. GRUPPI
;      REGISTRATION NUMBER:  37,341
;      REFERENCE/DOCKET NUMBER:  2026-4124US1
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (212) 758-4800
;      TELEFAX:  (212) 751-6849
;      TELEX:  421792
;  INFORMATION FOR SEQ ID NO:  84:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  9
;      TYPE:  amino acid
;      STRANDEDNESS:  Unknown
;      TOPOLOGY:  Unknown
;    MOLECULE TYPE:  Peptide
US-08-417-174-84

  Query Match             100.0%;  Score 45;  DB 1;  Length 9;
  Best Local Similarity   100.0%;  Pred. No. 1e+06;
  Matches    9;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 IMDQVPFSV 9
              |||||||||
Db          1 IMDQVPFSV 9
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SEQ ID No:3

```
RESULT 1
US-08-417-174-104
; Sequence 104, Application US/08417174
; Patent No. 5844075
;  GENERAL INFORMATION:
;    APPLICANT:  KAWAKAMI, YUTAKA; ROSENBERG,
;    APPLICANT:  STEVEN A.
;    TITLE OF INVENTION:  MELANOMA ANTIGENS AND
;    TITLE OF INVENTION:  THEIR USE IN DIAGNOSTIC AND THERAPEUTIC
;    TITLE OF INVENTION:  METHODS
;    NUMBER OF SEQUENCES:  126
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  MORGAN & FINNEGAN, L.L.P.
;      STREET:  345 PARK AVENUE
;      CITY:  NEW YORK
;      STATE:  NEW YORK
;      COUNTRY:  USA
;      ZIP:  10154
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  FLOPPY DISK
;      COMPUTER:  IBM PC COMPATIBLE
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  ASCII
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/417,174
;      FILING DATE:  05-APR-1995
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/231,565
;      FILING DATE:  22-APR-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  CAROL M. GRUPPI
;      REGISTRATION NUMBER:  37,341
;      REFERENCE/DOCKET NUMBER:  2026-4124US1
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (212) 758-4800
;      TELEFAX:  (212) 751-6849
;      TELEX:  421792
;  INFORMATION FOR SEQ ID NO:  104:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  9
;      TYPE:  amino acid
;      STRANDEDNESS:  Unknown
;      TOPOLOGY:  Unknown
;    MOLECULE TYPE:  Peptide
US-08-417-174-104

  Query Match             100.0%;  Score 49;  DB 1;  Length 9;
  Best Local Similarity   100.0%;  Pred. No. 1e+06;
  Matches    9;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 YLEPGPVTV 9
              |||||||||
Db          1 YLEPGPVTV 9
```

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Kawakami et al. regarding the DNA

encoding immunogenic peptides derived from melanoma antigen gp100, including SEQ ID No: 2 and SEQ ID No:3 recited in claims 24-26 and 36 of instant application, into the combined teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton et al. directing to : A method for treating melanoma comprising: (a) administering to a mammal having melanoma a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the mammal develops an immune response against the tumor antigen; and, (b) subsequently administering at least 10 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal, to arrive at the claimed inventions as recited in claims 24-26 and 36.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Kawakami et al. on the DNA encoding DNA encoding immunogenic peptides derived from melanoma antigen gp100, including SEQ ID No: 2 and SEQ ID No: 3, into the combined teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton et al. because Kawakami et al. teaches that gp100 is a well-established melanoma tumor antigen and SEQ ID No: 2 and SEQ ID No: 3 are immunogenic to induce anti-melanoma T cells mediated immune response.

There would have been a reasonable expectation of success given (i) combinatory cancer therapy with expression of a tumor antigen and expression of a cytokine (including INFγ) either co-administered or sequentially administered, by the teachings of Paoletti, (ii) identification of multiple melanoma-associated antigen and expression of nucleic acid encoding the antigens in treating melanoma, by the teachings of Emtage et al. (Examples 1-4), (iii) the results of high dose of INF-α2b in the treatment of melanoma by the teachings of Kirkwood et al. to achieve a

tumor antigen specific immune response involving enhanced T cell response, (iv) various combinations of vaccine therapy protocols for treating malignant melanoma, immunogenic antigens identified in human melanoma cells, and subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 melanoma patients who failed Melacine treatment regardless of their HLA phenotype, by the teachings of Morton et al. (See title, Table 1, and page 233), and (v) generation of cytotoxic T lymphocytes (CTL) immune response by administering nucleic acid encoding gp100, by the teachings of Kawakami et al. (See Example 3)

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and ***Response to Applicant's arguments***

Applicants state that Applicants' position with respect to the combination of Paoletti, Kirkwood, Emtage, and Morton. disclosures were set forth in the preceding section, and are maintained with respect to these rejections. The Office Action alleges that Kawakami teaches gp I00 peptides but does not suggest that the reference can substitute for Morton's alleged teaching of vaccine & cytokine combination therapies. Accordingly, the reference cannot be used in combination with Paoletti, Kirkwood, and Emtage to support a proper *prima facie* case of obviousness regarding the instantly pending claims. It is therefore requested that these rejections be withdrawn.

In response, the reasons for combining the teachings of Paoletti, Kirkwood, Emtage, and Morton have been clearly documented in the maintained rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37 under 35 U.S.C. 103(a) as being unpatentable over Paoletti (U.S. patent number 5,942,235) in view of Emtage et al. (US 2003/0113919), Kirkwood et al. (2001), and Morton et al. (1996). Kawakami et al. is relied on for the teachings of immunogenic peptides derived from melanoma antigen designated gp100, including SEQ ID No: 2 and SEQ ID No: 3 recited in claims 24-26 and 36 of instant application (See the alignment of SEQ ID No: 2 of

instant application with SEQ ID No: 84 of Kawakami et al., and the alignment of SEQ ID No: 3 of instant application with SEQ ID No: 104 of Kawakami et al.).

7. Claims 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Paoletti** (U.S. patent number 5,942,235; issued on August 24, 1999; this reference has been cited in the office action mailed on 07/25/2006) in view of **Emtage et al.** (US 2003/0113919, publication date 06/19/2003, filed on 08/15/2002, provisional applications 60313438, 60313572, 60313573, 60313574 filed on 08/17/2001; this publication has been cited as reference A64 in the IDS filed by Applicant on 03/22/2010), **Kirkwood et al.** (Kirkwood et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol.* 19(9): 2370-80, 2001; this reference has been cited in the office action mailed on 07/25/2006), and **Morton et al.** (Morton et al., Vaccine therapy for malignant melanoma, *CA Cancer J Clin.* 46(4):225-44, 1996), as applied to claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37 above, and further in view of **Kuvshinoff et al.** (Kuvshinoff et al., Computed tomography in evaluation of patients with stage III melanoma, *Ann Surg Oncol.* 4(3):252-8, 1997). *This rejection is necessitated by claim amendments filed on 06/14/2011 by Applicant.*

Amended claim 1 filed on 06/14/2011 reads as follows: A method for treating melanoma comprising: (a) administering to a mammal having melanoma a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the mammal develops an immune response against the tumor antigen; and, (b)

subsequently administering at least l0 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal.

Amended claim 38 filed on 06/14/2011 reads as follows: The method of claim 1 further comprising examining the mammal to identify evidence of melanoma progression following step (b).

Amended claim 39 filed on 06/14/2011 reads as follows: The method of claim 38 wherein the mammal is examined radiologically.

The teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton have been discussed in the preceding section of the rejection of claims 1, 4-7, 11-15, 18-22, 28-30, 32-35 and 37 under 35 U.S.C. 103(a) as being unpatentable over Paoletti in view of Emtage et al., Kirkwood et al., and Morton et al.

None of Paoletti, Emtage et al., Kirkwood et al. and Morton et al. teaches identification of evidence of melanoma progression by radiological examination recited in claims 38 and 39.

However, at the time of filing of instant application, identification of evidence of melanoma progression by radiological examination was known in the art. For instant, **Kuvshinoff et al.** teaches that Metastatic disease is detected infrequently by computed tomography (CT) in early stage melanoma. The diagnostic yield of routine CT for stage III melanoma is less established, despite extensive use in clinical practice. Kuvshinoff et al. teaches that charts from 347 asymptomatic patients with stage III melanoma were reviewed. *Findings suggestive of metastatic melanoma identified by head or body CT, chest radiography, bone scan, or liver function studies were confirmed histologically or by progression of disease.* Kuvshinoff et al. concludes that routine CT in patients with clinical stage III melanoma infrequently identifies metastatic disease. Head CT in the asymptomatic patient, chest CT in patients with

groin adenopathy, and pelvic CT in the presence of axillary or cervical adenopathy are not indicated. Selective use of chest CT in patients with cervical adenopathy or pelvic CT in the presence of groin disease may be useful (See page 252, Kuvshinoff et al., 1997).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Kuvshinoff et al. regarding computed tomography in evaluation of patients with stage III melanoma and metastatic melanoma identified by head or body CT, chest *radiography*, bone scan, or liver function studies were confirmed histologically or by progression of disease, into the combined teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton et al. directing to a method for treating melanoma comprising: (a) administering to a mammal having melanoma a composition comprising a nucleic acid encoding a melanoma-associated tumor antigen as the sole active pharmaceutical agent such that the mammal develops an immune response against the tumor antigen; and, (b) subsequently administering at least l0 MU/m^2/day interferon alpha 2b (IFN-α2b) as the sole active pharmaceutical agent to the mammal, to arrive at the claimed inventions as recited in claims 38 and 39.

One having ordinary skill in the art would have been motivated to incorporate the teachings of Kuvshinoff et al. on computed tomography in evaluation of patients with stage III melanoma and metastatic melanoma identified by head or body CT, chest *radiography*, bone scan, or liver function studies were confirmed histologically or by progression of disease, into the combined teachings of Paoletti, Emtage et al., Kirkwood et al., and Morton et al. because Kuvshinoff et al. clearly teaches that radiological examination is used in clinical practice to

monitor and evaluate the treatment of melanoma at various stages, especially in the context of disease progression of metastatic melanoma.

There would have been a reasonable expectation of success given (i) combinatory cancer therapy with expression of a tumor antigen and expression of a cytokine (including INFγ) either co-administered or sequentially administered, by the teachings of Paoletti, (ii) identification of multiple melanoma-associated antigen and expression of nucleic acid encoding the antigens in treating melanoma, by the teachings of Emtage et al. (Examples 1-4), (iii) the results of high dose of INF-α2b in the treatment of melanoma by the teachings of Kirkwood et al. to achieve a tumor antigen specific immune response involving enhanced T cell response, (iv) various combinations of vaccine therapy protocols for treating malignant melanoma, immunogenic antigens identified in human melanoma cells, and subsequent administration of interferon alfa-2b (IFN alpha-2b) at a dose of $5x10^6$ U/m^2 subcutaneously, three times per week, induced responses in eight of 18 melanoma patients who failed Melacine treatment regardless of their HLA phenotype, by the teachings of Morton et al. (See title, Table 1, and page 233), and (v) the demonstration of metastatic melanoma identified by head or body CT, chest radiography, bone scan, or liver function studies were confirmed histologically or by progression of disease, by the teachings of Kuvshinoff et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

8. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632